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Effectiveness of Immunomodulators in Perineal Crohn's Disease: Moroccan Experience and Literature Review

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Abstract

We describe the evolution of patients with perineal Crohn's disease (PCD) treated with immunomodulators (IM): the purine anti-metabolites or methotrexate (MTX) in the absence of biotherapy**.** This was a retrospective descriptive study including all patients with (PCD) treated with (IM) and who cannot get biotherapy. The evaluation of the response was based on clinical response and / or morphology. Overall, 62 patient were under (IM). a good result was observed in 63% with complete healing in 79.2% and a partial response in 20.8%. The response time was variable with a median of 4 **[**2-24**]** months. Our study shows that despite the progress of biotherapy, the purine anti-metabolites retain their place in the treatment of Crohn's disease in general and in (PCD) more specifically.

Keywords: Perineal Crohn's disease, immunomodulators, azathioprine, 6-mercaptopurine, Metothrexate.

INTRODUCTION

Perineal Crohn's disease (PCD) is common, it's affect one out of two patients during the course of Crohn's disease (CD) and are considered as a criterion of severity. They are often chronic and / or recurrent, with a risk of recurrence reported in the literature between 23% to 59% at 2 years. Their localizations in the terminal part of the digestive tract, their influence on the control of continence and the proximity of the genital tract, make them very uncomfortable, which affect the quality of life and increase the morbidity. The therapeutic approach of (PCD) has made great progress since the advent of biotherapy, however the place and the effectiveness of the (IM) is not yet clear.

The aims of this work is to report our experience with patients with perineal manifestation treated with immunomodulators (IM) (purine agents or methotrexate) in the absence of biotherapy and on the other hand to demonstrate that immunomodulators can be a good waiting alternative especially in low income countries which can give very good results.

PATIENTS AND METHODS

This is a retrospective descriptive study, from January 1990 to April 2024.

Inclusion Criterion: All patients with perineal Crohn's disease treated with (IM) who can not have biotherapy.

Exclusion Criteria: Patients treated with combo therapy.

The description of the MAP in this study was according to Cardiff's classification and topography of the luminal disease according to the Montreal classification.

At first a Drainage of the suppurative lesions with oral antibiotic therapy (quinolones and / or metronidazole) is done if necessary before initiating the basic treatment.

The prescribed doses of IM were: 2 to 2.5mg / kg for AZA and 1 to 1.5 mg / kg for 6-MP and if no response to purine agents: MTX 25µg / week intramuscularly for 12 weeks then 15µg / week in intramuscular.

The evaluation of the response was based on clinical response because of the easy clinical accessibility of these lesions easily complemented by anoscopy (improvement in drainage, tenderness, induration, fistula closure, ulceration healing) and

morphology (pelvic MRI or endo-anal ultrasound (EUS)).

Therapeutic surveillance included a complete blood count every week during the first month and then every month for 3 months and then at least every 3 months. The Liver function tests (ALAT-GGT-Alkaline phosphatase) is prescribed at the beginning and at least every 3 months.

The dosage of AZA was adjusted in case of lymphopenia (500/mm3) or neutropenia (1500/ mm3), or cytolysis or cholestasis and 6-Thioguanine nucleotide levels were tested if necessary.

The improvement under treatment was defined by the closure of the fistulas and a complete healing of the ulcerations (complete response) and the reduction of at least 50% of the drained fistulas with reduction of the pain and induration felt by the patient (partial response).

Failure was defined by the absence of improvement of symptoms, reopening of an old fistula or the appearance of a new lesion.

Statistical Analysis:

For descriptive statistical analysis, the qualitative variables are expressed as numbers and percentages and quantitative variables are expressed as means and standard deviations (± SD) if the variable is normally distributed or median and interquartiles if the variable is not normally distributed.

For comparison between the two independant groups of responders and nonresponders we used the khi-2 test for qualitative variable and t-student for quantitative variable. p-value < 0.05 is considered as statically significant.

The analysis was carried out by the SPSS Software.

RESULT

Of a total of 167 patients with (PCD), 62 patients were under (IM). We describe characteristics of our study populations through (Table 1). The age was 32 +/- 10,42 with extremes [15-71] with a female predominance 39 (62,9 %). The time of diagnosis of (PCD) was variable: 35.5% in the same time of luminal disease, 53.2% occurred during disease progression and only 11.3% preceded the disease. The predominant topography of the luminal disease is L2: 46.8% and rectal involvement was present in 67.7% (42 cases). The incidence of elemental lesions was as follows: Anal fistulas were present in 97.8% (60 cases), ulcerations in 35.4% (20 cases), and stenoses in 19.4% (12 cases).

Therapeutically, at first ano-perianal fistulas benefited surgical drainage with antibiotic therapy (Metronidazole +/- Quinolone) and the cases of stenosis benefited from finger dilation with the average of 3 to 4 sessions (case by case). In the maintenance phase 60.7% (37/62) were on azathiopirine, 23% (14/62) on 6-MP, 16.4% (10/62) on MTX after thiopurines. A good overall result was noted in 63% (34 cases) with complete cicatrization in 79.2% (29 cases) and a partial response in 20.8% (05 cases). (Table 2) The response time was variable with a median of 4 [2-24] months. Failure was noted in 37% (20 cases), 27.3% (3 cases) of these patients benefited from temporary fecal diversion and 36.4% (4 cases) had a definitive stoma. Adverse effects occurred in 6 patients: 1 case of haematotoxicity under AZA leading to MTX, 3 cases of haematotoxicity under 6-MP leading to MTX in two patients and AZA in one patient. A case of allergic reactions to 6-mercaptopurine, has been put under methotrexate, and a case of repeated superinfection of DDB leading to the definitive suspension of the treatment.

Comparison between responders and nonresponders found out that the absence of stenosis and the absence of rectal involvement were more present in responders with a difference statically significant ($p < 0.05$) (table 3), regardless of age, the sexe, the moment of apparition of the perianal disease, the topography of LD ($p > 0.05$).

After 06 years of follow-up, monitoring of responders was possible in 15 patients (44,11%), 12 patients maintained the response, including 1 case who switched to anti-TNF for luminal relapse.

A relapse was noted in 3 patients, one of whom ended up with a definitive ileostomy and 02 patients placed on anti-TNF.

Table 1: General data of the population studied

Number of patients	62
Average age (years)	32 +/- 10,42
Sex (female)#	39 (62,9)
Time of diagnosis # Before LD Concomitant with LD After LD	 7 (11,3) 33 (53,2) 22(35,5)
delay of response (month)* (responders)	 4 **[**2-24**]**

Topography # (montreal classification)	
L1	24 (38,7)
L2	29 (46,8)
L3	9 (14,5)
Rectal involvement #	
Absent	20 (32,3)
Present	42 (67,7)
Frequency of anal lesions #	
Fistula	60 (97.8)
Ulcerations	20 (35.6)
Stenosis	12(19.4)
Treatment #	
AZA	37 (59,7)
6-MP	14 (22,6)
MTX	2 (3,2)
thioprine then MTX	8 (12,9)
Evolution #	
Bonne	34 (54,8)
Echec	20 (32,3)
Lost to follow-up	8 (12,9)

LD: luminal disease; *median and interquartile; #Expressed as number and percentage

Table 2: Distributions of elementary lesions and their evolution under treatment

	Number of cases *	**good response***
Fistula		
F1a	33(53,2)	18 (52,9
F1b	5 (8,1)	2 (5,9
F1c	4(6,5)	1 (2,9
F2a	2 (3,2)	1 2,9
F2b	0	0
F2c	15 (24,2)	7 20,6
F2d	1 (1,6)	0
Ulceration		
U1a	11(17,7)	8 (23,5)
U1b	2(3,2)	1(2,9)
U1c	1(1,6)	1 (2,9)
U2a	2 (3,2)	1(2,9)
U2c	4(6,5)	1(2,9)
stenosis		
S1a	4(6,4)	2 (5,9)
S1b	2 (3,2)	2 (2,9)
S1c	1(1,6)	0
S2a	5(8,1)	0
S2c	0	0

**Expressed as number and percentage*

Table 3: Comparison between responders and non responders

Factors	**Responders***	**Non Responders ***	**P-Value**
Âge	32+/-11,54	28,70+/-8,36	0,273
Sex (Femele)	20(58,8%)	15 (75%)	0,229
Moment De Diagnostic			
1	22 (64,7)	7 (35)	0,1
2	9 (26,5)	9(45)	
3	3(8,8)	4(20)	
Topography Dela Maladie			
L1	13(38,2)	8(40)	0,74
L2	15(44,1)	10(50)	
L3	6(17,6)	2(10)	

Stenosis			
S1a	2 (5.9)	1 (5)	,891
S1b	2 (5.9)	0	,269
S1c	0	0	
S 2a	0	5(25)	**0.002**
S 2c	0	0	-
Rectal involvement	18(52.9)	17(85)	**0.017**

**Expressed as number and percentage*

DISCUSSION

Ano-perineal lesions can occur at any time during the course of Crohn's disease, and even precede intestinal disease for many years, and in very rare cases can remain isolated as the unique manifestation of the disease. Their overall prevalence in the population with Crohn's disease is highly variable and remains approximate and poorly evaluated reported between 22 % and 82% and are more frequent and severe than the disease is distal [1]. To date, there does not appear to be a significant difference neither in geographical terms nor in terms of age and sex. However, Markowitz (1995) reported a particular entity, to which he attributed the name "highly destructive perianal disease" and in which he found greater morbidity and a significant racial factor (the black race) [2].

According to the Hughes classification, three types of MAP are defined:

- The primary lesion (type I) (U) correspond to inflammatory lesions (cavitating ulcerations, extensive ulcerations, gross skin tags, and fissures); they reflect the activity of intestinal disease.
- Secondary lesion (type II) (F) are due to infection of primary ulcerative lesions (abscesses and fistulas); they appear during flares of CD that persist in remission.
- Secondary mechanical lesion (type III) (S) are scarring lesions that develop between flares of intestinal disease, and progress for their own purpose.

To this UFS classification is added an appendix classification related to the associated lesions to the associated lesions, the whole being known as the Cardiff classification [3].

The treatment of PCD is a real challenge, and often requires close collaboration between gastroenterologists, proctologists and surgeons. There is still no consensus on the management of anal lesions in CD. Only infliximab has demonstrated, through large randomized controlled trials, a medium- and long-term efficacy in the management of ano-perineal fistulas. As for the efficacy of conventional immunosuppressive agents (thiopurines, methotrexate), no prospective randomized study has investigated the benefits of azathioprine, 6-mercaptopurine or methotrexate on perineal Crohn's disease. Thiopurines are analogues of the purine bases, which act by their active metabolite 6-Thioguanine Nucleotide (6 TGN). AZA is often preferred to 6MP because of its better oral availability (50% vs. 25%). In the randomized controlled trial of Present *et al.*, (1980) [4] comparing the efficacy of 6-MP with placebo in 83 patients with active CD luminal, perineal disease persisted significantly less often in patients treated with 6MP than in those receiving placebo: 6-mercaptopurine (1.5 mg / kg) resulted in complete closure of the fistula in 9 of 29 patients (31%) versus 1 of 17 (6%) in the placebo group. A partial response was shown in 7 of 29 patients (24%) compared to 3 of 17 patients (18%) who received placebo. In this study, the average response time was 3.1 months. Thus, the overall response rate (partial and complete response) was 55% for patients who received (6-MP) versus 24% for patients receiving placebo. In a subgroup of 29 patients with perianal fistulas, 24% of patients had a partial response and 31% had a complete response. The same team [5] published 5 years later a prospective, double-blind, uncontrolled study of 26 perineal fistulas (18 cases of anal fistula, 6 cases of recto-vaginal fistula, 2 cases of vulvar fistula): after a minimum treatment of 6 month, 39% of fistulas were healed (6 cases of anal fistula, 2 cases of recto-vaginal fistula) and 26% has improved (4 cases of anal fistula, 1 case of recto-vaginal fistula, 1 case of vulvar fistula). The average response time was 3.1 months, with 23% of patients taking more than 4 months to show any response. There were no side effects, but relapses in large numbers of patient at the end of treatment. Korelitz *et al.*, [6] (1993), after 20 years of clinical experience with 6-mercaptopurine (6-MP) in 148 patients with Crohn's disease who did not respond enough to steroids and / or other medical treatments. Healing or improvement of peri rectal fistulas and abscesses was noted in 87% of cases ($p < 0.05$). The uncontrolled retrospective study of O'Brien *et al.*, [7] involving 78 patients treated with AZA or 6-MP gave very similar results. Twenty-six patients had 35 fistulas, a complete closure of all fistulas was noted in 31% of patients and 54% had a partial response. The meta-analysis by Pearson *et al.*, (1995) [8] reviewing nine studies [1966-1994] on the efficacy of AZA in placebo-controlled crohn's disease found as secondary objective, complete or partial closure of fistulas in 54% of patients treated (22 / 41), versus 21% receiving placebo (6/29) with an odd ratio of 4.44. In another study that is both retrospective and prospective, Camus *et al.*, (2013) [9] investigated the rate and duration of relapses in patients without corticosteroids after one year of AZA therapy (n

= 220), compared to a population of patients who did not receive immunosuppressive medications in this period (n = 440). In the AZA-treated population, the cumulative 10-year remission rate was 38%. As a secondary objective, the authors noted that treated patients had a decreased risk of 2/3 of anal surgery compared to the control population.

More recently, a Cochrane systematic literature review and meta-analysis of 03 randomised controlled trials for azathioprine or 6-mercaptopurine induction therapy, including only 18 patients, 54% (6/11) of azathioprine patients had a fistula response compared to 29% (2/7) of placebo patients (RR 2.00, 95% CI 0.67 to 5.93). This finding was statistically insignificant [10].

Markowitz *et al.*, [11] describes the effect of 6-mercaptopurine on a younger population of patients with an average age of 16.5 years. They found a beneficial effect, with the incidence of perianal lesions decreasing from 78% to 47% after treatment, this being particularly pronounced on fistulas (from 40% to 14%); and as a result the percentage of patients without PCD increased from 22% to 53%. This effect occurred in 50% of patients in the first 6 months of treatment. An equivalent result was found in the series of C. DEJACO [18].

In the pediatric population, the purine anti-metabolites may also be effective in the treatment of perineal Crohn's disease. In a retrospective study of 15 children with Crohn's disease perianal treated [1987-1997] [12] for ≥ 6 months with 6-MP or AZA, the PDAI increased to 4.4 from an initial value of 7, 7. The improvement is statistically significant (p <0.001). An improvement in fistulas was noted in 40% of cases: One patient (7%) had complete fistula resolution and five patients (33%) had a marked decrease in fistula size.

In a retrospective analysis, Lecomte *et al.*, [13] investigated predictors of perineal Crohn's disease response including fistulas, fissures, and stenosis to 6-MP or AZA. They found that patients aged 40 and older, with the recent onset of perianal disease and without a fistula [14], responded better to treatment. No relationship was found between perineal evolution and intestinal response to AZA or 6-MP. (Table 4) summarizing the literature data outcomes about perianal crohn disease and immunomodulator (thiopurines or MTX).

Table 4: The response to immunomodulators in the literature

Series	**molecules**	**Year of publications**	**Delay of response** (month)	**Number of cases**	**Complete Response***	**partial Response***	**global Response***
Present *et al.*, 1980 [4]	6-MP	1980(7 years)	3,1(0,5-9)	29	9 (31)	7(24)	16(55)
Korelitz *et al.*, 1985 [5]	6-MP	1985(2 years)	3,1 (0,5-4)	26	8(39)	6(26)	14(65)
Korelitz *et al.*, 1993[6]	6-MP	1993(20 years)	—--		--	--	87%
O'Brien *et al.*,1991[7]	AZA or 6-MP	1991(10 years)	19,2	24	8(33,33)	10(41,6)	18(75)
Pearson *et al.*, 1995 [8]	AZA	[1966-1994]	—-	41	--	---	22(54)
Jeshion WC, 2000 [12]	AZA or 6-MP	[1987-1997]	> 6	15	1(7)	5(33)	6(40)
Lecomte *et al.*, 2003 [13]	AZA or 6-MP	2003	—-	94	–	–	27 (29)
C. DEJACO2003 [18]	AZA	2003	3,1	29	9	8	17(48)
Notre série	AZA or 6-MP or MTX	2018	4(2-24) month	54	29(30,6)	5(8,1)	34(63)

**Expressed as number and percentage*

On these arguments, thiopurines have long been the preferred medical treatment of ano-perineal lesions of crohn's disease until the advent of biotherapies. The essential disadvantage of these molecules is their inertia which doesn't allow evaluating their real effectiveness after several weeks of treatment. They are therefore not well adapted to the management of PCD in the acute phase but rather to maintain a remission. Methotrexate is used as a third-line therapeutic agent for patients who are intolerant to azathioprine and 6-mercaptopurine. No controlled prospective study has studied the use of this drug for perineal lesions. Mahadevan *et al.*, [15] retrospectively evaluated the efficacy of MTX monotherapy (15-25 mg / week IM for a minimum of 3 months) in patients with intolerance or AZA / 6-MP failure; 33 patients received MTX, 16 (48%) for fistulising luminal disease. Clinical remission was achieved in 62% of treated patients. The median response time was 6 weeks. Of the 16 patients with fistulas; the response was complete in 4 cases and partial in 5 cases, giving a response rate of 56%. Relapse was frequently observed in case of dose reduction or oral relay.

The limitation of all these studies is that they do not have as their main objective the treatment of perineal disease and that this parameter is not taken into account in the initial stratification, and that some are old at a time

when the doses of the treatment used were lower. After an adequate clinical and radiological evaluation. The medical treatment must be put in place without delay, either after a conservative drainage surgery or immediately in the absence of suppuration. Antibiotics, as primary therapy, are recommended, but by no means sufficient.

The need for a stoma or a proctectomy can be up to 50% for complexes and stenosing fistulas in the absence of biotherapies.

The fecal diversion by an enterostomy (ileostomy or upstream colostomy) is sometimes proposed as a "waiting solution" for young patients suffering from severe PCD (in the hope of improving the lesions allowing secondarily the closure of the bypass stoma). Overall, the chances of a secondary recovery of continuity after diversion of fecal remain low but vary according to the lesions. Proctectomy is decided as a last resort after failure of other medical and surgical treatments. Especially in case of severe lesion (complex fistula, rectovaginal fistula or anal stenosis) with incontinence associated with significant rectal lesions (microrectum). Rectal amputation does not always resolve the perineal problems of patients and delayed healing is common [16].

Nowadays PCD management is still a challenge. The biotherapy Like anti-TNF and more recently ustekinumab after anti-TNF failure or the use mesenchymal stem cell injection might be effective but the failure rate is significant so more studies or novel therapeutic strategies are needed [17].

Limitations of our Study

The retrospective study design could induce a bias of selection and a bias of gathering information. However, the data were collected prospectively and made these biases minimal. A large randomized study is needed but in the era of biotherapy is ethically impossible.

CONCLUSION

The (MAP) in the context of Crohn's disease are frequent, their care require medical and surgical collaboration, specialized and experienced. The pre-therapeutic evaluation must be exhaustive, including magnetic resonance imaging or endo-anal ultrasound, rectosigmoidoscopy and most often an examination under general anesthesia. It is probably legitimate to propose biotherapy because only these molecules act quickly and their effectiveness is demonstrated but 60% of the patients relapse after one year of anti-TNF therapy [17]. However, immunomodulators remain an alternative, especially in countries with low income, which can give very good results up to complete healing and maintenance of a long-lasting remission. It should also be stressed the importance of conservative surgical treatment that optimizes medical treatment.

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